Progress in human TB vaccine development

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BCG

- Live attenuated *M. bovis*
- First used in 1921 (per os)

**Efficacy:**

- Good
  - Disseminated TB and TB meningitis
  - Leprosy

- Bad
  - Lung disease – at any age
  - Boosting (Rodrigues et al, Lancet 2005)
BCG Protective Efficacy – Meta analysis

- 70 trials; spanning 46 years
- Efficacy of 0% - 80%
- Average reduction in incidence of 50%
- Latitude has major influence on efficacy
Why doesn’t BCG work?

• Different strains of BCG
• Nutrition

• Exposure to environmental mycobacteria
  – Masking (Black et al, 2002)
  – Blocking (Brandt et al, 2002)
Design of an improved vaccine against TB

• Include BCG in new regime

• Needs to induce cellular immune response

• 3 possible strategies:
  
  – Boost BCG with a subunit vaccine
    
    • Protein + adjuvant
    
    • Viral vector
  
  – Replace BCG with improved BCG / attenuated *M. tb*
  
  – Boost an improved BCG
# Global TB Vaccine Pipeline

## Phase I
- **AERAS-422**
  - Aeras
  - [P](#)
- **AdAg85A**
  - McMaster University
  - [P](#), [B](#)
- **Hyvac 4/ AERAS-404**
  - SSI, Sanofi-Pasteur, Aeras, Intercell
  - [B](#)
- **SSI H56-IC31**
  - SSI, Aeras, Intercell, TBVI
  - [P](#), [B](#), [P](#)

## Phase II
- **M72+AS01**
  - GSK, Aeras
  - [B](#), [P](#)
- **RUTI**
  - Archivel Farma
  - [B](#), [P](#), [P](#)
- **VPM 1002**
  - Max Planck, Vakzine Projekt Mgmt, TBVI
  - [B](#)
- **Hybrid-1+IC31**
  - SSI, TBVI, EDCTP, Intercell
  - [P](#), [B](#), [P](#)

## Phase IIb
- **MVA85A/ AERAS-485**
  - Oxford-Emergent Tuberculosis Consortium (OETC), Aeras
  - [B](#), [P](#)
- **AERAS-402/ Crucell Ad35**
  - Crucell, Aeras
  - [B](#)

## Phase III
- **Mw [M. indicus pranii (MIP)]**
  - Dept of Biotechnology (India), M/s. Cadila
  - [IT](#)

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### TB Vaccine Types
- **Viral-vectored:** MVA85A, AERAS-402, AdAg85A
- **Protein/adjuvant:** M72, Hybrid-1, Hyvac 4, H56
- **rBCG:** VPM 1002, AERAS-422
- **Killed WC or Extract:** Mw, RUTI

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*Source: Tuberculosis Vaccine Candidates – 2010; Stop TB Partnership Working Group on New TB Vaccines*  
*With updates from sponsors*
### Global TB Vaccine Pipeline

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*With updates from sponsors*
Modified vaccinia Ankara (MVA)
- Poxvirus
- No replication in mammalian tissues
- Good T cell boosting vector
- Excellent safety record

*M. tb* antigen 85A
- Mycolyl transferase
- Major target antigen
- Protective in small animals
- In all environmental mycobacteria
- Doesn’t interfere with new diagnostic tests

BCG - MVA85A regimen
MVA85A can improve BCG induced protection in preclinical animal models

MICE

Goonetilleke et al, JI 2003

GUINEA PIGS

Williams et al, I&I 2005

CATTLE

NHP

Verreck et al, PLoS ONE 2009

Vordermeier M et al, I&I 2009
MVA85A can improve BCG induced protection in preclinical animal models

MICE
- Goonetilleke et al, JI 2003

NHP
- Verreck et al, PLoS ONE 2009

GUINEA PIGS
- Williams et al, I&I 2005

CATTLE
- Vordermeier M et al, I&I 2009
Data from cattle challenge to suggest that Ag85A-specific cultured ELISPOT responses correlate with protection

Experimental design (n = 10/group)
- Control group
- BCG (week 1)
- BCG (week 1)/MVA-85A (week 6)
- BCG (week 1)/Adeno-85A (week 6)
- Cultured ELISPOT at week 14
- *M. bovis* i.t. challenge at week 14
- PM at week 28

Vordermeier I&I 2009
In vitro Ag85A-induced IFN-γ and IL-17 pre-challenge correlate with protection.

qRT-PCR of various cytokines pre and post challenge.

Vordermeier et al, I&I 2009
Safety and efficacy of MVA85A, a new tuberculosis vaccine, in infants previously vaccinated with BCG: a randomised, placebo-controlled phase 2b trial

Michele D Tameris*, Mark Hatherill*, Bernard S Landry, Thomas J Scriba, Margaret Ann Snowden, Stephen Lockhart, Jacqueline E Shea, J Bruce McClain, Gregory D Hussey, Willem A Hanekom, Hassan Mahomed†, Helen McShane†, and the MVA85A 020 Trial Study Team

www.thelancet.com Published online February 4, 2013 http://dx.doi.org/10.1016/S0140-6736(13)60177-4

• The first efficacy trial with a new TB vaccine in infants since BCG
  • Developed in 1921, last tested in infants in 1968

• The first efficacy trial of a subunit TB vaccine

• Only 1 other candidate TB vaccine evaluated in efficacy in recent years (M vaccae in HIV+ adults)
Trial design

• All infants HIV and \textit{M.\textit{tb}} negative at enrolment

• All infants got BCG within 7/7 of birth

• Infants randomised to MVA85A (1 x 10^{8} pfu) or placebo (candin) @ 4-6/12

• All infants followed up 3 monthly after enrolment until study completed

• Any child with TB exposure/symptoms admitted to CV ward for investigation

• Trial powered on TB disease to see 60% improvement over BCG alone (with 90% power)

• \textit{M.\textit{tb}} infection endpoint using QFT conversion
### Primary and secondary efficacy endpoints

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo (n=1395)</th>
<th>MVA85A (n=1399)</th>
<th>Vaccine Efficacy % (95% CI)</th>
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<td><strong>Endpoint #1 (Primary Efficacy Endpoint)</strong></td>
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<td></td>
<td>17.3% (-31.9 to 48.2)</td>
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<tr>
<td>39 (2.8)</td>
<td>32 (2.3)</td>
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<tr>
<td><strong>Endpoint #2 (Exploratory Efficacy Endpoint)</strong></td>
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<td>-6.9% (-56.1 to 26.9)</td>
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<tr>
<td>52 (3.7)</td>
<td>55 (3.9)</td>
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<tr>
<td><strong>Endpoint #3 (Exploratory Efficacy Endpoint)</strong></td>
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<td></td>
<td>-12.1% (-37.4 to 8.5)</td>
</tr>
<tr>
<td>177 (12.7)</td>
<td>196 (14.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>QFT conversion:</strong></td>
<td>171</td>
<td>178</td>
<td>-3.8% (-28.1 to 15.9)</td>
</tr>
</tbody>
</table>

Tameris M et al, Lancet 2013
Correlate samples

• PBMC & serum from each infant pre-vaccination and 28 days post-vaccination

• June 2012 meeting with all stakeholders

• Agreed list of assays – wet lab work complete

• Data analysis ongoing
Assays for immune correlates of risk analysis

Transcriptional analysis
• Illumina HT12 arrays
• RNA Seq
• Fluidigm/qPCR for biomarkers identified in BCG infant study*

Functional Assays
• Growth inhibition assays with BCG and MTB

Immune Assays
• IFN-γ ELISPOT assays (UNS, PHA, BCG, 85A)
• Antibodies on serum samples
• Luminex on supernatants from above assays*

Cellular phenotyping
• Cell surface flow cytometry for lymphoid and myeloid cells
• Markers of activation, exhaustion, T cell regulation*
• ICS flow cytometry for IFN-g, TNFα, IL2, IL17*

*Secondary assays to be performed on stored supernatant, RNA, frozen/fixed cells

Fletcher H et al unpublished
We need to design some more potent vaccines

• New routes of immunisation
  – Aerosol

• Prime - boost combinations
  – Ad-M combinations

• New antigens
An inhaled TB vaccine

- Route of immunisation = route of infection
- BCG does not reliably protect against pulmonary TB
- Mucosal immunisation can generate potent durable immune responses
- Inhalation is a common route of drug delivery
- Feasible
- Needle and pain free
- Murine data to support this route of immunisation
- Not a new idea!
Assessing the inhaled route in a human clinical trial

• Phase I trial
  – 22 BCG vaccinated adults randomised to $1 \times 10^7$ pfu MVA85A inhaled or ID
  – Randomised single blinded paired placebo design
  – Bronchoscopy day 7 BAL

Primary and secondary outcome
  – Safety: local & systemic AEs, $S_aO_2$, spirometry, bronchoscopy
  – Systemic and mucosal cellular immunogenicity: blood and BAL
Combination vaccines

• TB032
  – Aeras 402 prime – MVA85A boost in BCG-vaccinated UK adults
  – 3 groups:
    • AM; AAM; AAA
    • Fully enrolled

• TB034
  – ChAdOx1.85A prime – MVA85A boost in BCG-vaccinated UK adults
  – Low dose safety cohort – enrolment complete
  – Then 24 subjects randomised to C alone or C prime – M boost
  – Study ongoing
We need better models to evaluate candidate vaccines
Human mycobacterial challenge models

• An effective vaccine against BCG should also protect against *M. tuberculosis*

• Does intradermal BCG ‘challenge’ provide a good model for aerosol *M. tuberculosis* challenge?
  – Validation in preclinical animal models
Pilot BCG challenge study

- BCG (SSI), $2-8 \times 10^5$ cfu/100ul
- Route i.d
- Sampling: 4mm punch biopsy
- Biopsy at 1, 2, or 4 weeks post BCG

Minassian A et al, JID 2012
BCG challenge results for BCG and MVA85A vaccination

A = naïve
B = MVA85A
C = BCG
D = BCG-MVA85A

* p < 0.05
** p < 0.01
*** p < 0.001

Harris S et al, JID 2013
Summary

• Progress has been made
  – Efficacy trials are feasible; 1 completed, another soon to start

• Urgent need for better models to evaluate vaccines
  – Preclinical – cattle, particularly natural transmission model
  – Clinical – human mycobacterial challenge models

• Use every opportunity to identify potential correlates
  – Validate correlates identified in cattle studies

• Use human efficacy data to review and refine models
Acknowledgements

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